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Brief Report

Physical Frailty and Hemoglobin-to-Red Cell Distribution Width Ratio in Japanese Older Outpatients

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Abstract

The Frailty screening should be widely performed; however, simple and inexpensive biomarkers are missing. Biomarkers that can be routinely assessed in many patients are desirable. Recently, the hemoglobin-to-red cell distribution width ratio (Hb/RDW, HRR) has been suggested as a new prognostic marker and has been reported to be associated with inflammation, one of the factors contributing to frailty. Therefore, we aimed to address the role of HRR in frailty among 557 older outpatients (aged 65–96 years). Frailty was assessed using the Japanese version of the Cardiovascular Health Study criteria, and HRR was calculated from clinical records. Participants were classified into five groups based on a sex-stratified quintile of HRR (Q1–Q5). Of the participants, 20.3% were frail. Using multiple logistic regression models with the Q5 group as a reference, after adjusting for sex, age, body mass index, polypharmacy, pre-orthopedic surgery, and the use of iron medications, the multivariable-adjusted odds ratios (95% confidence intervals) of the Q4 to Q1 groups were 0.92 (0.58–1.47), 1.04 (0.67–1.61), 1.29 (0.84–1.96), and 1.85 (1.22–2.82), respectively, indicating that a lower HRR was significantly associated with frailty. The robustness of these results was also shown in the multiple imputation analysis. The results suggest that HRR measurement may be one of the indicators to identify frail older adults in routine practice.

Key words: Hemoglobin, red cell distribution width, frailty, biomarker, screening.

Introduction

Frailty screening should be performed for all older adults in daily practice. To achieve this goal, a biomarker obtained from a routine blood examination may be beneficial for the screening that identifies patients who should be assessed for frailty, including physical assessment. This is because blood examinations are conducted routinely and can be performed without requiring large space, expensive instruments, or additional cost.

A complete blood count (CBC) is a routine blood examination, and includes hemoglobin (Hb) and red cell distribution width (RDW). Both lower Hb levels and higher RDW have been reported to be associated with frailty (1-4), and the possible mechanism is systemic inflammation, which is one of the factors involved in the onset and progression of frailty (5, 6). Inflammation increases hepcidin level, which regulates iron metabolism and decreases blood iron levels, leading to lower Hb levels (7, 8). Further, inflammatory cytokines inhibit erythropoietin synthesis, shorten the erythrocytes lifespan, and increase the release of immature red blood cells, resulting in increased RDW (8-11).

Recently, Sun et al. suggested the peripheral Hb-to-RDW ratio (HRR) as a novel inflammatory marker (12). The first study on the ability of HRR to predict frailty was conducted by Qu et al. in 2021, in which they showed that HRR was more predictive for frailty than only Hb or RDW in hospitalized patients with coronary heart disease (10). However, to the best of our knowledge, no study has investigated the association between HRR and frailty other than the report by Qu et al. Therefore, it is necessary to investigate whether the association between HRR and frailty can be reproduced in different settings. We investigated the association between HRR and frailty in older outpatients.

Methods

Study design and participants

This cross-sectional study included participants of the Frailty Registry Study, which was conducted on outpatients of a frailty clinic in a general geriatric hospital in Aichi, Obu, Japan. In total, 595 participants without disabilities, which was defined with a Katz index score ≥5 (13), who visited the clinic between June 2017 and May 2020, were initially included. The eligibility criteria for the present study were as follows: (i) age ≥65 years and (ii) no history of erythropoietin administration. Finally, data from 557 participants were analyzed.

This study was approved by the Ethics Committee of Human Research of the National Center for Geriatrics and Gerontology, Japan (No. 881–11), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Frailty assessment

Physical frailty was assessed using the Japanese version of the Cardiovascular Health Study criteria (J-CHS), which has

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Table 1. Participants' characteristics

	HRR*					P-value	
	Q1 (n=112)	Q2 (n=112)	Q3 (n=115)	Q4 (n=107)	Q5 (n=109)		
Range: Male	Q1 0.36 to 0.86	Q2 0.87 to 0.95	Q3 0.96 to 1.05	Q4 1.06 to 1.12	Q5 1.13 to1.44		
/Female	Q1 0.38 to 0.81	Q2 0.82 to 0.899	Q3 0.90 to 0.95	Q4 0.96 to 1.04	Q5 1.05 to 1.22	Diff.†	Trend‡
Male, n%	36 (32.1)	36 (32.1)	37 (32.2)	36 (33.6)	36 (33.0)	0.999	
Age, year	80.3±5.6	78.0±6.2	77.2±5.9	77.6±5.7	75.4±5.8	<0.001	<0.001
BMI, kg/m^2	22.5±4.0	23.3±4.5	24.2±5.0	24.2±3.8	24.3±3.9	0.005	<0.001
Number of medications	6.2±3.3	6.0±3.4	5.4±3.5	5.4±3.6	4.2±3.3	<0.001	<0.001
Polypharmacy, n%	74 (66.1)	71 (63.4)	65 (56.5)	58 (54.2)	44 (40.4)	0.001	
Pre-orthopedic surgery patients, n%	31 (27.7)	34 (30.4)	23 (20.0)	18 (16.8)	15 (13.8)	0.011	
Use of iron medications, n%	9 (8.0)	3 (2.7)	0 (0.0)	0 (0.0)	1 (0.9)	<0.001	
Gate speed, m/sec	1.3±0.4	1.4±0.4	1.5±0.5	1.5±0.4	1.7±0.5	<0.001	<0.001
Grip strength, kg							
Male	27.9±7.6	28.5±5.7	30.6±6.6	29.7±6.7	32.9±6.1	0.014	0.007
Female	18.7±4.8	20.4±5.1	20.9±4.6	20.7±4.6	21.7±5.2	0.004	0.001
Hb, g/dL	10.8±1.1	12.1±0.8	12.7±0.8	13.5±0.8	14.3±1.0	<0.001	<0.001
RDW, %	15.4±2.7	13.8±0.8	13.4±0.6	13.1±0.6	12.6±0.6	<0.001	<0.001

*HRR = Hb/RDW; † P-values were obtained using one-way ANOVA for continuous variables and the $\chi 2$ test for categorical variables; ‡ P-values were obtained using the Jonckheere-Terpstra test; HRR, hemoglobin-to-red cell distribution width ratio; Q, quintile; Diff, difference; BMI, body mass index; Hb, hemoglobin; RDW, red cell distribution width; ANOVA, analysis of variance.

five components (shrinking, weakness, slowness, exhaustion, and low activity) and was based on the original criteria of the phenotype model proposed by Fried (14-16). The criteria were optimized for older Japanese adults and validated elsewhere (15-17). Frailty was defined as having three or more components, and pre-frailty was defined as having one or two components.

HRR calculation

Hb and RDW were obtained from the CBC, and the HRR was calculated by dividing Hb by RDW. Blood samples were collected at the first visit to a frailty clinic.

Covariates

Body mass index (BMI; kg/m^2) was calculated using anthropometric data. Polypharmacy was defined as ≥5 medications based on clinical records. Participants with pre-orthopedic surgery and iron medication were identified from clinical records.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD), while categorical variables are presented as numbers and percentages (%). Participants were classified into five groups according to the sex-stratified quintile of HRR (Q1–Q5). The characteristics of the participants in these groups were compared using a one-way analysis of variance and the Jonckheere-Terpstra test for continuous variables, and the $\chi 2$ test for categorical variables.

Both complete-case and imputation-case analyses were analyzed. In the imputation-case analysis, the multiple imputation method was used to handle missing data with 20 imputed datasets using Rubin's formula (18). In both complete-case and imputation-case analyses, with the Q5 group as reference, the associations between HRR and frailty, and between HRR and pre-frailty and frailty (i.e., J-CHS≥1) were analyzed using multiple logistic regression models. Covariates of model 1 were sex, age, BMI, and polypharmacy and those of model 2 were model 1 plus pre-orthopedic surgery, and the use of iron medications. Additionally, as a supplemental analysis, the associations between HRR (as a continuous variable) and five components of frailty were analyzed using multiple logistic regression models with the same covariates.

All statistical analyses were performed using the IBM SPSS Statistics ver. 28.0 (IBM Japan, Tokyo, Japan), and statistical significance was indicated by two-sided P-values<0.05.

Results

The missing values were as follows: gate speed (included in the five criteria of J-CHS), n=1; blood examination (including Hb and RDW), n=2. None of the covariate data was missing.

The mean ± SD (range) of age was 77.7 ± 6.0 (65–96) years. Among the 556 participants who had complete J-CHS data, 113 (20.3%) were frail and 328 (59.0%) were pre-frail. Participants were significantly younger, had a higher BMI, fewer medications, higher gate speed, and higher grip strength from the Q1 group to the Q5 group (Table 1).

The multivariable-adjusted associations of HRR with pre-frailty and frailty are shown in Table 2. The OR for frailty was significantly higher in the Q1 group than in the Q5 group. This significant association was also observed for pre-frailty and

Table 2. Multivariable-adjusted association of HRR with pre-frailty and frailty (n=555)*

	For Frailty (J-CHS ≥3)								
	Crude			Model 1			Model 2		
	OR	95%CI	P-Value	OR	95%CI	P-Value	OR	95%CI	P-Value
HRR†									
Q5 (case, n=8)	Ref.			Ref.			Ref.		
Q4 (case, n=18)	0.90	0.57-1.42	0.647	0.91	0.57-1.45	0.701	0.92	0.58-1.47	0.736
Q3 (case, n=22)	1.05	0.69-1.61	0.818	1.04	0.67-1.62	0.848	1.04	0.67-1.61	0.876
Q2 (case, n=25)	1.41	0.94-2.12	0.097	1.36	0.89-2.06	0.152	1.29	0.84-1.96	0.243
Q1 (case, n=35)	2.11	1.43-3.09	<0.001	1.83	1.22-2.75	0.003	1.85	1.22-2.82	0.004
Male	0.72	0.45-1.14	0.157						
Age	1.06	1.03-1.10	0.001						
BMI	1.00	0.95-1.05	0.980						
Polypharmacy	2.48	1.57-3.92	<0.001						
Pre-orthopedic surgery	1.91	1.20-3.04	0.006						
Using of iron preparations	0.33	0.04-2.54	0.285						
	For Pre-frailty and Frailty (J-CHS ≥1)								
	Crude			Model 1			Model 2		
	OR	95%CI	P-Value	OR	95%CI	P-Value	OR	95%CI	P-Value
HRR†									
Q5 (case, n=64)	Ref.			Ref.			Ref.		
Q4 (case, n=86)	1.05	0.68-1.62	0.841	1.07	0.69-1.67	0.761	1.10	0.70-1.72	0.692
Q3 (case, n=93)	1.02	0.67-1.55	0.941	1.02	0.67-1.58	0.911	1.04	0.67-1.61	0.863
Q2 (case, n=93)	1.34	0.85-2.12	0.205	1.26	0.79-2.01	0.323	1.18	0.74-1.90	0.490
Q1 (case, n=96)	2.00	1.20-3.35	0.008	1.82	1.07-3.10	0.027	1.76	1.02-3.06	0.044
Male	0.85	0.55-1.30	0.444						
Age	1.04	1.10-1.08	0.021						
BMI	0.99	0.95-1.04	0.709						
Polypharmacy	2.78	1.81-4.25	<0.001						
Pre-orthopedic surgery	2.56	1.38-4.74	0.003						
Using of iron preparations	0.87	0.24-3.22	0.835						

*ORs and 95% CIs were estimated using the multiple logistic regression analysis. Model 1: adjusted for sex, BMI, and polypharmacy. Model 2: adjusted for pre-orthopedic surgery, and using of iron preparations in addition to the variables in model 1; †HRR = Hb/RDW; J-CHS, the Japanese version of the Cardiovascular Health Study criteria; OR, odds ratio; CI, confidence interval; HRR, hemoglobin–to–red cell distribution width ratio; Q, quintile; BMI, body mass index; Hb, hemoglobin; RDW, red cell distribution width.

frailty (i.e., J-CHS ≥1). The results of the multiple imputations showed the robustness of these complete case analyses.

In the supplemental analysis, the odds ratios (ORs) and 95% confidence intervals (CIs) of HRR for each of the five components of frailty were as follows: in model 1, shrinking 0.05 (0.01–0.21), P<0.001; exhaustion 0.83 (0.26–2.67), P=0.753; low activity 0.06 (0.02–0.21), P<0.001; slowness 0.09 (0.02–0.47), P=0.005; and weakness 0.28 (0.08–0.98), P=0.046. In model 2, shrinking 0.06 (0.01–0.24), P<0.001; exhaustion 0.51 (0.15–1.78), P=0.294; low activity 0.10 (0.03–0.36), P<0.001; slowness 0.06 (0.01–0.42), P=0.004; and weakness 0.06 (0.01–0.42), P=0.004. The robustness of these results was also shown in the multiple imputation analysis.

Discussion

This study clarified that a lower HRR was significantly associated with pre-frailty and frailty in older outpatients. This significance remained even after adjusting for polypharmacy and pre-orthopedic surgery, both of which had a significantly positive association with frailty in the univariate analysis. Polypharmacy and orthopedic diseases are common challenges in older patients, but these results suggest that HRR may be used to screen frailty independent of these problems. HRR can be calculated from Hb and RDW included in the CBC, which is a routine blood test, and is also suggested as a novel prognostic marker because it could theoretically reflect health conditions, including the nutritional status, inflammatory condition, and immune function (12). Our findings indicate that using HRR for frailty screening may be helpful for routine assessments.

This study had 20.3% frail older adults. It has been reported that the prevalence of frailty in Japanese community dwellers aged 75–79, 80–84, and ≥85 years is 10%, 20.4%, and 35.1%, respectively (19). The prevalence of frailty was slightly higher in this study than in recent studies, possibly because the present study was conducted on outpatients at a frailty clinic.

In the association between HRR and components of the frailty phenotype, HRR was significantly associated with four of five components, i.e., shrinking, low activity, slowness, and weakness, but was not associated with exhaustion. Exhaustion is also a main symptom of depression and has been suggested to be positively associated with frailty (20, 21). Furthermore, sleep disorders and poor sleep quality generally manifest as exhaustion, and an association between sleep problems and frailty has been reported (22, 23). Thus, HRR may not always reflect exhaustion due to other causes, such as depression and sleep disorders. However, Qu et al. suggested that HRR is the most optimal screening marker compared to only Hb or RDW, based on receiver operating characteristic analysis (10). Although lower Hb and anemia may decrease tissue oxygenation, reduce muscle synthesis and strength, and cause frailty (24, 25), previous studies have reported sex differences in the association between Hb and frailty (26, 27). Of note, RDW is considered an indicator of cellular senescence, i.e., telomere shortening (28) and a marker of inflammation (11). Thus, HRR, which is a combined index of Hb and RDW, may reflect frailty more strongly than each marker alone. It is reasonable to routinely check HRR for screening individuals for frailty at outpatient clinics.

The present study has some limitations. First, this was a single-center study, and the participants were limited to outpatients of a frailty clinic in Japan. Future studies in other settings are needed. Second, we investigated the association between HRR and frailty based on a cross-sectional study to consider whether HRR can be used to screen people who should be assessed for frailty. It is important to investigate the predictive ability of HRR for adverse outcomes in older people with a longitudinal study. Third, 13 of the participants in this study had taken iron medications. Given that iron medications increase Hb and decrease RDW (29), the HRR of those taking iron pills may be higher than the actual HRR level. Thus, the association between HRR and frailty in those participants may have been overestimated.

In conclusion, a lower HRR was significantly associated with pre-frailty and frailty based on the phenotype model among older Japanese outpatients. This suggests that using HRR to screen people who require a detailed evaluation for frailty, that is, using HRR as the first step for routine frailty screening, would provide an opportunity for frailty assessment in many older people.

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